

Atypical presentations of inclusion body myositis: Clinical characteristics and long-term outcomes

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Abstract

Introductions/Aims: Inclusion body myositis (IBM) typically presents with progressive weakness preferentially involving finger flexors and quadriceps. Atypical presentations have been less commonly reported. Here, we aim to describe the clinical characteristics and long-term outcomes of IBM patients with atypical presentations.

Methods: We retrospectively searched the Mayo Clinic medical records to identify IBM patients with atypical disease onset, seen between 2015 and 2020.

Results: We identified 357 IBM patients, of whom 50 (14%) had an atypical presentation. Thirty-eight patients were diagnosed with IBM because they fulfilled one of the European Neuromuscular Center diagnostic categories at a later stage, 10 had all IBM histopathological features, and 2 were diagnosed on the basis of clinical and laboratory data. The most common presentation was dysphagia (50%), followed by asymptomatic hyperCKemia (24%; CK, creatine kinase), then foot drop (12%). 6% of patients presented with proximal arm weakness, 4% with axial weakness and 4% with facial diplegia. Median time from symptom onset to diagnosis was 9 y. Median age at diagnosis was 70.5 y. 16% of patients needed a walking aid. When tested, 86.5% of patients had impaired swallowing and 56% had elevated cytosolic nucleotidase-1A antibodies. Only 1/26 patients who received immunotherapy had minimal improvement. Upon follow-up, most patients had generalization of their weakness with a decline in their strength summated score of 0.082/mo.

Discussion: A significant proportion of IBM patients may have an atypical presentation. Recognition of such heterogeneity could improve early diagnosis, prevent unnecessary immunotherapy, and provide insight for future diagnostic criteria development and clinical trials.

KEYWORDS

asymptomatic hyperCKemia, axial myopathy, dysphagia, foot drop, inclusion body myositis

Abbreviations: ANA, anti-nuclear antibody; CK, creatine kinase; cN-1A antibodies, cytosolic nucleotidase-1A antibodies; ELISA, enzyme-linked immunosorbent assay; EMG, electromyography; ENMC, European Neuromuscular Center; IBM, inclusion body myositis; IgG, immunoglobulin G; MRC, Medical Research Council; MRI, magnetic resonance imaging; MRS, modified Rankin Scale; SSS, Summated Strength Score; T-LGLL, T-cell large granular lymphocytic leukemia.

1 | INTRODUCTION

Inclusion body myositis (IBM) is the most common acquired muscle disease after the age of 50.¹ Clinically, it is characterized by an insidious onset and asymmetric weakness, predominantly affecting finger flexors and quadriceps.² This pattern of preferential muscle involvement is an essential element of diagnostic criteria for IBM, including



the most widely accepted 2011 European Neuromuscular Center (ENMC) criteria.³ While considered highly specific, different diagnostic criteria have varying degrees of sensitivity.⁴ The excellent specificity, nearing 100%, across all categories in most diagnostic criteria, stems in part from the pathognomonic combination of endomysial inflammation with invasion of nonnecrotic muscle fibers (autoaggressive inflammation), rimmed vacuoles, and protein aggregates in IBM.⁴ However, it is well recognized that patients with IBM can present with features beyond this classic presentation. Highlighting the wide spectrum of IBM presentations has relevance for clinical care and research. Clinically, recognition of atypical presentations would facilitate prompt diagnosis, and appropriate care, prognosis, and monitoring for complications. Furthermore, response to immunotherapy and long-term outcomes of atypical IBM remain unknown. From the standpoint of research and clinical trial readiness, the atypical presentations add another layer of variability to be accounted for, in a disease well-known to be heterogeneous.⁵ As the corresponding literature consists mostly of case reports or brief descriptions of atypical presentations in series focused on typical IBM, we sought in this study to systematically define the clinical and laboratory characteristics of IBM patients with atypical presentations, as well as report their long-term outcomes in a large single-center series of deeply-phenotyped patients.

2 | METHODS

2.1 | Patient selection

The study was approved by the Institutional Review Board at Mayo Clinic. The study was considered minimal risk; therefore, the requirement for informed consent was waived. However, records of any patient who had not provided authorization for their medical records to be used for research, as per Minnesota statute 144.335, were not reviewed. We retrospectively searched the Mayo Clinic electronic medical records to identify patients with IBM who were evaluated between January 01, 2015, and December 31, 2020. Typical IBM presentation consists of patients fulfilling one of the three categories in the ENMC 2011 diagnostic criteria: clinico-pathologically defined, clinically-defined, and probable IBM.³ Per these criteria, the typical pattern of weakness consists of preferential involvement of finger flexion more than shoulder abduction, or knee extension equal to or more than hip flexion. Therefore, we considered the following categories of disease onset as atypical: dysphagia, asymptomatic or minimally symptomatic hyperCKemia (CK, creatine kinase), and weakness affecting the distal lower limb, proximal upper limb, axial, or facial muscles. A patient had to have an atypical pattern of weakness at presentation to our clinic, or a well-documented atypical disease onset, supported by clear documentation of a detailed motor examination prior to presentation to our clinic. All patients had at least one muscle biopsy interpreted in our muscle laboratory. Muscle specimens at our institution are obtained via an open surgical biopsy. In the hyperCKemia group, we included patients who were asymptomatic or minimally

symptomatic, mainly reporting myalgia and cramps at onset, and who had a CK level above the upper limit of normal, accounting for age and race. To be included in our study, the patients with atypical presentation had to fulfill one of three predefined inclusion criteria: (1) fulfillment of the ENMC criteria at a later stage of their disease (any category); (2) pathologically defined diagnosis, requiring the presence of autoaggressive inflammation, rimmed vacuoles and protein aggregates; (3) the presence of both autoaggressive inflammation with either rimmed vacuoles or congophilic inclusions, with other cardinal IBM features not included in ENMC criteria (such as muscle magnetic resonance imaging [MRI] pattern, or cytosolic nucleotidase 1A [cN-1A] antibody status) after alternative causes had been exhaustively excluded. Testing for cN-1A antibodies, immunoglobulin G (IgG) isotype, was performed at a commercial lab (RDL reference laboratory, Los Angeles, CA) using enzyme-linked immunosorbent assay (ELISA).

Disease duration was defined as time from symptom onset to date of muscle biopsy. Muscle strength data were extracted from patients' medical records, and documented according to the Mayo Clinic scale: 0 equivalent to modified Medical Research Council (MRC) grade 5; −1 for MRC grade 4⁺; −2 for MRC grade 4; −3 for MRC grade 4[−]; −3.25 for MRC grade 3; −3.5 for MRC grade 2; −3.75 for MRC grade 1, and −4 for MRC grade 0. For outcome measures, we used quadriceps muscle strength (weaker side if asymmetric), summated strength score (SSS), the modified Rankin Scale (mRS), and the severity of dysphagia (mild, moderate, or severe) on swallowing evaluation. The SSS was calculated by summing the score on motor examination of bilateral shoulder abduction, elbow flexion and extension, finger flexion, hip flexion, knee extension, and foot dorsiflexion. The SSS ranges from 0 or normal to −56 (complete paralysis of these muscles bilaterally). The mRS score, used to assess the patient's level of disability, ranges from 0 (no symptoms) to 6 (dead) as follows: mRS: (1) symptoms without disability; (2) slight disability with ability to perform baseline activities; (3) moderate disability requiring some help, but able to walk unassisted; (4) moderately severe disability with inability to walk unassisted (wheelchair bound); and (5) severe disability with need for constant nursing care and bedridden.⁶ Dysphagia evaluations were performed by occupational or speech therapists, and included review of medical history, patient symptoms, assessment of oral motor control, phonation, respiratory control, and an oral intake trial.

We reviewed the patients' demographics and clinical characteristics; serological, electrodiagnostic, and histopathological data; and the results of swallowing function at time of presentation to our neuromuscular clinic. When follow-up was available, response to treatment was defined as improvement in strength documented by bedside strength assessment or improvement of dysphagia on swallowing evaluation.

2.2 | Statistical analysis

Data are expressed as proportions and percentages for categorical variables and median (range) for continuous variables. To avoid multiple comparisons, each group was compared against all the other

TABLE 1 Demographics and clinical characteristics

Features	All patients (n = 50)	IBM subtypes					
		Dysphagia (N = 25)	HyperCKemia (N = 12)	Foot drop (N = 6)	Proximal upper limb weakness (N = 3)	Axial weakness (N = 2)	Facial weakness (N = 2)
Demographics							
Females	29 (58%)	19 (76%)* ¹	4 (33.3%)	2 (33.3%)	1 (33.3%)	1 (50%)	2 (100%)
Age at symptom onset (y)	62 (20–80)	64 (42–77)	58 (20–76)	66.5 (32–80)	54 (49–67)	75.5 (72–79)* ⁹	46 (44–48)
Age at evaluation (y)	69 (40–83)	70 (55–82)	61.5 (40–76)	70 (44–83)	57 (53–72)	77 (75–79)	54.5 (46–63)
Age at diagnosis (y)	70.5 (40–86)	72 (57–82)	67.5 (40–77)	70.5 (44–86)	58 (53–73)	80.5 (80–81)* ¹⁰	56.5 (49–64)
Symptoms at diagnosis							
Myalgias or cramps	11 (22%)	2 (8%)* ²	7 (58.3%)* ⁵	1 (16.7%)	1 (33.3%)	0 (0%)	0 (0%)
Limb weakness	35 (70%)	21 (84%)* ³	3 (25%)* ⁶	5 (83.3%)	3 (100%)	1 (50%)	1 (50%)
Axial weakness	3 (6%)	2 (8%)	0 (0%)	0 (0%)	0 (0%)	2 (100%)	0 (0%)
Bulbar weakness	33 (66%)	25 (100%)* ⁴	3 (25%)* ⁷	1 (16.7%)* ⁸	1 (33.3%)	1 (50%)	2 (100%)
Weight loss	5 (10%)	4 (16%)	0 (0%)	1 (16.7%)	0 (0%)	0 (0%)	0 (0%)

Note: Categorical variables are presented as number of patients (percentage), continuous variables are presented as median (range). Numbers in bold are statistically significant when compared against other groups combined. *¹ $p = 0.0099$; *² $p = 0.0374$; *³ $p = 0.0322$; *⁴ $p < 0.0001$; *⁵ $p = 0.0017$; *⁶ $p = 0.0006$; *⁷ $p = 0.0012$; *⁸ $p = 0.0136$; *⁹ $p = 0.0422$; *¹⁰ $p = 0.0397$.

patients grouped together. The Fischer exact test/chi squared test and the Wilcoxon rank sum/Kruskal Wallis tests were used to compare categorical and continuous variables, respectively. Statistical analysis was performed using JMP version 14(SAS Institute, Cary, NC). All the tests were two-sided, and p value <0.05 was considered significant.

3 | RESULTS

3.1 | Baseline and clinical characteristics

We identified 357 patients who were diagnosed with IBM, of whom 307 (86%) had a typical IBM onset and were further categorized according to the 2011 ENMC criteria as follows: 196/357 (55%) clinico-pathologically defined, 66/357 (18%) clinically defined, and 45/357 (13%) probable IBM. Fifty (14%) IBM patients had an atypical disease onset. Thirty-eight patients were diagnosed with IBM as they fulfilled ENMC criteria at a later stage, and 10 had a pathologically-defined diagnosis. Of the remaining two patients, one had autoaggressive inflammation and multiple rimmed vacuoles (but no congophilic inclusions), quadriceps atrophy without weakness, marked distal involvement of the vastus medialis and vastus lateralis on muscle MRI and elevated cN-1A antibodies; the other had autoaggressive inflammation and several congophilic inclusions (but no rimmed vacuoles), dysphagia, and markedly elevated cN-1A antibodies. Of these 50 patients, the group presenting with dysphagia was the most common (50%), followed by hyperCKemia (24%) then foot drop (12%). Three patients (6%) presented with proximal upper limb-predominant weakness, two (4%) with axial weakness (one patient with head drop and another with camptocormia), and two (4%) with facial diplegia.

Baseline demographics and clinical characteristics of patients with atypical IBM are summarized in Table 1. Mean and median durations from symptom onset to diagnosis were 9 and 6 y, respectively, ranging from 1 up to 31 y. Patients presenting with dysphagia were more commonly females, and the two patients presenting with facial diplegia were both females. Patients presenting with axial weakness were older at symptom onset and diagnosis. Reported symptoms at time of diagnosis are shown in Table 1. Patients with dysphagia were more likely to report limb weakness at diagnosis (84% vs. 52% in other groups combined), and patients presenting with foot drop were least likely to report dysphagia (16.7% vs. 72.7%). The patients in the hyperCKemia group who reported dysphagia or limb weakness at time of diagnosis had clear documentation in their records of being asymptomatic and having no weakness on examination for a period of time prior to our evaluation.

Patients in the hyperCKemia group initially sought medical attention for either myalgia and fatigue (five patients), or for an incidentally elevated CK level (seven patients). The CK level was checked in asymptomatic patients for various reasons such as screening for statin complications or during a cardiac workup. Muscle biopsy was performed due to the persistently elevated CK level, in addition to the detection of a myopathy on electromyography (EMG), muscle abnormality on MRI, or elevated cN-1A antibody.

Clinical outcome measures at baseline are shown in Table 2. The group with proximal upper limb weakness had a significantly higher mRS score compared to other groups. At time of presentation, eight patients (16%) needed a walking aid. Swallowing evaluation was not available for three patients in the group with dysphagia; all three patients underwent evaluation for dysphagia outside of our institution, one of whom had a dilatation procedure. Associated autoimmune comorbidities were found in 14 patients (28%), most commonly

TABLE 2 Clinical outcome measures at baseline and upon follow-up

Features	IBM subtypes						
	All patients (n = 50)	Bulbar (N = 25)	Asymptomatic (N = 12)	Foot drop (N = 6)	Proximal upper limb weakness (N = 3)	Axial weakness (N = 2)	Facial weakness (N = 2)
At first evaluation							
mRS	1 (0, 4)	1 (0, 4)	0.5 (0, 3)* ¹	1 (1, 2)	2 (1, 3)* ³	1.5 (1, 2)	1 (1, 1)
SSS	−8 (−41, 0)	−10 (−41, 0)	0 (−26, 0)* ²	−7.25 (−23, −2)	−18 (−19.75, −6)	−6 (−12, 0)	−13 (−23, −3)
Quadriceps strength	0 (−3.25, 0)	0 (−3.25, 0)	0 (−2, 0)	0 (−1, 0)	0 (−2, 0)	−0.5 (−1, 0)	0 (0, 0)
At follow-up							
Follow-up available	30	14	8	5	2	1	0
mRS	2 (0, 4)	1 (0, 4)	2 (0, 4)	2 (1, 2)	1, 2	2	NA
SSS	−13.875 (−38, 0)	−12.625 (−29, −3)	−14.125 (−31.25, 0)	−17.750 (−38, −3.5)	−6 and −19.75	−15.	NA
Quadriceps strength	−1 (−3.5, 0)	−1 (−3.5, 0)	−1.5 (−3.25, 0)	−1. (−2, 0)	0, 0	−1.	NA

Note: Continuous variables are presented as median (range). Numbers in bold are statistically significant when compared against other groups combined. *¹ $p = 0.0011$; *² $p = 0.0087$; *³ $p = 0.0340$. Abbreviations: mRS, modified Rankin scale; SSS, summated strength score.

Sjogren syndrome ($n = 6$) followed by rheumatoid arthritis ($n = 2$). There was no statistically significant difference in the frequency of autoimmune disorders among the groups: nine (64%) in those with dysphagia, three in patients with hyperCKemia, and two in the limb girdle group. Among these 14 patients, 3 of 7 who were tested had positive cN-1A antibodies (all with dysphagia). No patient had history of hepatitis C.

3.2 | Laboratory findings

3.2.1 | Serological tests

The findings are summarized in Table 3. All patients but one had at least one creatine kinase (CK) level available to review. CK elevation was found in 84% of patients ranging from 1.1 to 14.3 times upper limit of normal. There was no significant difference in CK levels between groups. Among patients with positive cN1A antibodies, 10 (71%) had moderately (40–80 units) or strongly (>80 units) positive titers. Twelve of 25 tested patients (48%) had positive anti-nuclear antibody (ANA), and 6 of 22 tested (27%) had positive SSA and/or SSB antibodies. Eighteen patients were tested for myositis autoantibody panel, and only 1 had weakly positive PL-7 and Ku antibodies: this patient had an onset of proximal upper limb weakness and had all classic pathological features (endomyal inflammatory infiltrate focally invading non-necrotic muscle fibers, rimmed vacuoles, and congophilic inclusions) on muscle biopsy. He received multiple trials of immunotherapy without improvement. Of 14 patients tested, 3 (21%) had evidence of T-cell large granular lymphocytic leukemia (T-LGLL) clone on T-cell gene rearrangement testing and/or flow cytometry.

3.2.2 | Electrodiagnostic testing

All patients had electrodiagnostic evidence for a myopathy except four (three with dysphagia and one hyperCKemia), three of whom had needle EMG showing long duration and high amplitude motor unit potentials in scattered muscles, leading to interpreting the findings as neuropathic at first. Results are summarized in Table 3. Most patients had fibrillation potentials. Myotonic discharges were found in nearly one third of patients. Short duration and low amplitude motor unit potentials were seen diffusely in most muscles examined. 23 (46%) patients had mixed short duration/low amplitude (myopathic) and long duration/high amplitude (neuropathic) motor unit potentials within the same muscle. The distribution of the myopathic motor unit potentials (axial, upper or lower limb, or diffuse) was not significantly different between groups (data not shown).

3.2.3 | Histopathology

Five patients (10%) required two biopsies to establish a histopathological diagnosis. Among patients with no appreciable weakness, muscle

TABLE 3 Laboratory and swallowing evaluation findings

		IBM subtypes					
Features	All patients (n = 50)	Bulbar (N = 25)	HyperCKemia (N = 12)	Foot drop (N = 6)	Proximal upper limb weakness (N = 3)	Axial weakness (N = 2)	Facial weakness (N = 2)
Serology							
CK elevation	41/49 (84%)	21/24 (87.5%)	12/12 (100%)	3/6 (50%)	2/3 (66.7%)	½ (50%)	2/2 (100%)
CK ULN	2.3 (1–14.3)	2.1 (1–14.3)	2.95 (1.1–12.8)	2.1 (1.2–8.7)	2.1 (2.1–2.1)	3.1 (3.1–3.1)	4.9 (1.8–8)
Anti- cN1A	14/25 (56%)	5/12 (42%)	4/5 (80%)	3 (50%)	0/2 (0%)	2/2 (100%)	2/2 (100%)
EMG							
Myopathy	46 (92%)	23 (92%)	10 (83.3%)	6 (100%)	3 (100%)	2 (100%)	2 (100%)
Fibrillation potentials	44 (88%)	23 (92%)	9 (75%)	6 (100%)	1 (33.3%)	1 (50%)	2 (100%)
Myotonic discharges	17 (34%)	7 (28%)	4 (33.3%)	4 (66.7%)	1 (33.3%)	0 (0%)	1 (50%)
Neuropathy	5 (10%)	3 (12%)	1 (8.3%)	0 (0%)	0 (0%)	1 (50%)	0 (0%)
Pathology							
Auto-aggressive inflammation	49 (98%)	24 (96%)	12 (100%)	6 (100%)	3 (100%)	2 (100%)	2 (100%)
Rimmed vacuoles	38 (76%)	16 (64%)	11 (91.7%)	5 (83.3%)	3 (100%)	2 (100%)	1 (50%)
Congophilic inclusions	36 (72%)	15 (60%)	11 (91.7%)	5 (83.3%)	3 (100%)	1 (50%)	1 (50%)
COX negative fibers	45 (90%)	24 (96%)	10 (83.3%)	6 (100%)	3 (100%)	1 (50%)	1 (50%)
Denervation	25 (50%)	9 (36%)	10 (83.3%)*¹	2 (33.3%)	1 (33.3%)	2 (100%)	1 (50%)
Swallowing assessment							
Available	37	22	5	4	3	1	2
Oropharyngeal dysphagia	32 (86.5%)	22 (100%)*²	4 (80%)	3 (75%)	1 (33.3%)	0 (0%)	2 (100%)
Cricopharyngeal bar	21 (56.8%)	16 (64%)*³	3 (60%)	1 (25%)	0 (0%)	0 (0%)	1 (50%)

Note: Categorical variables are presented as number of patients (percentage), continuous variables are presented as median (range). Numbers in bold are statistically significant when compared against other groups combined. *¹ $p = 0.0181$; *² $p = 0.0069$; *³ $p = 0.0233$.

Abbreviations: CK, creatine kinase; cN1A, cytosolic 5'-nucleotidase 1A; COX, cytochrome c oxidase; EMG, electromyography; ULN, upper limit of normal.

biopsy was guided by electrodiagnostic testing and/or muscle MRI. Thirty-two patients (64%) had all three pathological features of IBM (autoaggressive inflammation, rimmed vacuoles, and congophilic inclusions). Endomysial inflammation was the most common pathological feature, whereas rimmed vacuoles and congophilic inclusions were absent in 24% and 28% of patients, respectively. Cytochrome C oxidase negative fibers were observed in most patients. Denervation atrophy was more common in the hyperCKemia group compared to other groups combined. The data are summarized in Table 3.

3.2.4 | Others

Muscle MRI with and without contrast was performed in seven patients. Four patients had the classic pattern of muscle atrophy with fatty infiltration, and to a lesser extent T2 hyperintensity with mild post-contrast enhancement, affecting both vastus medialis and lateralis, with a proximal-to-distal gradient, predominantly affecting the distal portion of the muscles. One patient with dysphagia had a normal upper limb MRI. One patient from the hyperCKemia group had normal thigh MRI. One patient from the proximal upper limb weakness group had mild patchy T2 hyperintensity and atrophy in scattered thigh

muscles. Genetic testing was performed in 14 patients (28%) and showed no pathogenic mutations in any patient. Genetic testing included one or more of the following: screening for oculopharyngeal muscular dystrophy, myotonic dystrophy type two, facioscapulohumeral dystrophy, mitochondrial DNA analysis, or an expanded myopathy gene panel.

3.3 | Treatment response and long-term outcomes

Thirty-six patients (72%) patients had follow-up evaluations at our institution at 2–216 mo after initial presentation, with a median of 42 mo. Thirty (60%) patients had a documented examination at last follow-up. Patients' clinical scores upon presentation and follow-up are summarized in Table 2 and their SSS progression over time is shown in Figure 1. Regression line for the drop in SSS over time is also shown in Figure 1 with a slope of -0.082 (per month). Follow-up was not available for patients with facial diplegia. Twenty-six patients (52%) received immunosuppressive or immunomodulatory therapies. Of these, 46% received more than one agent. Reasons to initiate treatment included uncertainty about the diagnosis or misdiagnosis (mainly as polymyositis), uncertainty about treatment outcomes in

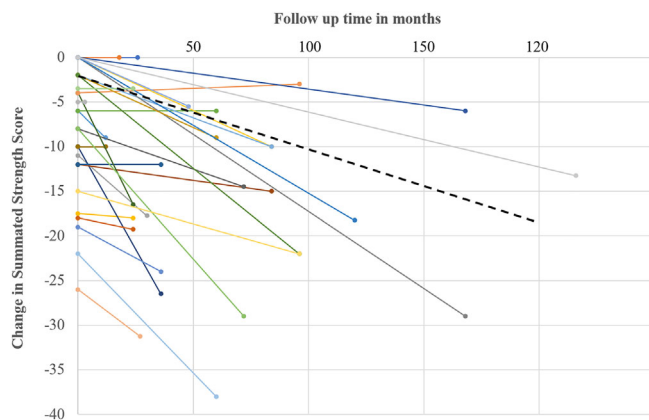


FIGURE 1 Change in SSS over time in inclusion body myositis patients with atypical presentation. Each patient is represented by an individual line. The dashed black line represents the linear regression of the drop of SSS over time. SSS, summated strength score.

atypical presentations of IBM, or some providers' preference to do a trial of immunotherapy in IBM patients before determining lack of responsiveness. Therapies included prednisone, methotrexate, azathioprine, mycophenolic acid, cyclosporine, rituximab, and intravenous immunoglobulin. Median duration of treatment was 12 mo (1–120 mo). Seven treated patients (27%) self-reported benefit either in limb weakness or dysphagia. However, only one patient, treated with prednisone and methotrexate, had an objective, but mild, treatment response, mostly with her dysphagia. This patient presented with dysphagia and had minimal weakness of proximal and distal upper limb muscles on first evaluation with an SSS of -4 . She received prednisone for 6 mo and methotrexate for 8 y. Her dysphagia improved upon follow-up from moderate in severity on swallowing evaluation to mild. Her last SSS was -3 .

Among patients who had an atypical onset, 38 (76%) patients eventually met the 2011 ENMC diagnostic criteria for IBM upon follow-up. The rest did not meet these criteria either due to lack of weakness or due to absence of the typical pattern of weakness. In the HyperCKemia group, seven patients eventually developed typical IBM weakness, whereas two patients had persistently normal strength at last follow-up. No follow-up was available in the remaining three patients. There was no significant difference between groups in their mRS score, SSS, or quadriceps strength at last clinical evaluation.

4 | DISCUSSION

Although excluded from all available diagnostic criteria, patients with atypical presentation constitute a significant proportion of IBM patients: 14% in our study and 8.8%–14% in previous reports.^{7,8} Diagnostic criteria serve to identify homogeneous populations for clinical trials, but the diagnosis in clinical practice should be based on integrating clinical, histopathological, imaging, and serological data. Hence, recognizing atypical presentations of IBM is important, as these patients may be misdiagnosed with other inflammatory myopathies,

or may undergo unnecessary immunotherapy. This is well reflected in our study given the long time from symptom onset to diagnosis, 9 y on average. This is the highest reported time to diagnosis; the mean time from symptom onset to IBM diagnosis in most epidemiological studies ranges from 4.1 to 5.6 y,^{9–12} and 8 y in one study.¹³ IBM should be considered in all patients over the age of 50 y who present with slowly progressive weakness or elevated CK levels, as it is the most common myopathy in this age group. In addition to the typical pattern of weakness when present, marked dysphagia, asymmetry of the weakness, elevated cN-1A antibodies, and proximal-to-distal fatty infiltration of the vastus medialis and lateralis on muscle MRI (more pronounced distally) should strongly raise suspicion for the disease. Muscle biopsy remains the gold standard to establish a diagnosis, especially in those with an atypical presentation.

As far as patients' demographics, IBM is known to predominantly affect males, with reported male-to-female ratios varying from 1.3 to 6.5.^{2,7,10,13–18} It is unclear why patients presenting with dysphagia were predominantly females (77%), a finding infrequently reported in previous studies.^{7,19,20} Of interest, our two patients who presented with facial diplegia were both females and it had been observed that females tend to have more severe facial weakness than males.⁷

Dysphagia is a well-known symptom of IBM,²¹ and it is associated with morbidity and mortality due to aspiration,^{20,22,23} as well as a lower quality of life.²⁴ In our study, 7% of patients of all IBM patients had dysphagia as a presenting symptom, a frequency similar to a previous report.²¹ The presence of a cricopharyngeal bar on video-fluoroscopy is not uncommon in IBM,²⁵ which frequently leads to obstruction-related dysphagia and increased risk for aspiration pneumonia.²⁶ This is not pathognomonic for IBM however, as a cricopharyngeal bar can be encountered in other inflammatory myopathies, inherited myopathies and with aging.^{27,28} Nevertheless, recognition of this finding may result in earlier interventions to improve outcomes. In our study, a cricopharyngeal bar was found in 64% of patients with dysphagia onset, which led to cricopharyngeal myotomy or balloon dilatation in all patients. These interventions can be of symptomatic benefit,^{20,29} but their effect on survival among IBM patients is yet to be shown. Last, IBM should be suspected in at-risk patients presenting with isolated dysphagia. Screening for associated subtle limb muscle involvement via motor examination, electrodiagnostic studies, and muscle imaging, and checking for CK elevation and cN-1A antibodies should be considered.

HyperCKemia with or without minimal symptoms constituted the second most common subgroup among atypical IBM patients. Although only two cases of IBM presenting with asymptomatic hyperCKemia were previously reported,^{30,31} this group is probably underestimated. It is noteworthy that the concept of prodromal disease is increasingly recognized in other neurological disorders³²; such view serves earlier interventions in therapeutic trials. This group of IBM patients could be of particular interest should biomarkers and disease modifying therapies become readily available in the foreseeable future.

Less common presentations of IBM included camptocormia, head drop, proximal upper limb weakness, or facial diplegia. Similar rare

cases have been reported.^{33–38} One of the IBM patients presenting with head drop was included in our recent publication of myopathies presenting with head drop, in which IBM constituted about 2% of cases (2 of 107).³⁹ Axial muscles are commonly overlooked, and when examined, they are frequently involved in myopathies.⁴⁰ In such cases, evaluating muscles in proximity to axial muscles, such as pharyngeal and respiratory muscles, should be considered due to their higher risk of involvement.³⁹

Despite their atypical presentation, most patients had significant morbidity at time of diagnosis, such as dysphagia, gait impairment, and falls requiring the use of a walking aid. Similar to typical IBM, all patients showed no response to treatment, except one patient with mildly improved dysphagia. Dysphagia is the only feature of IBM with anecdotal evidence of response to immunotherapy,^{41–43} and correlation with endomysial inflammation on muscle biopsy.⁴⁴

Last, like typical IBM,⁴⁵ most patients experienced progression and generalization of their weakness over time. The marked variability in progression rate found in our series is a well-known feature of typical IBM.^{5,46–48} Furthermore, the variable disease onset site can be associated with a variable morbidity profile, which is well highlighted in this study. Identifying reliable and valid clinical outcome measures has been a challenge.⁵ The atypical presentations of IBM further extend the heterogenous nature of the disease.

Limitations of this study include its retrospective design, referral bias inherent to tertiary care centers, lack of follow-up in some patients, absence of sensitive clinical assessment tools to better assess disability among patients in different groups, and lack of a uniform diagnostic and treatment response evaluation.

In summary, a significant proportion of IBM patients may present in an atypical fashion, most frequently with early dysphagia, asymptomatic hyperCKemia, or foot drop. Awareness of such a wide range of IBM presentations could facilitate early recognition and diagnosis. Future development of diagnostic criteria and outcome measures should take into consideration this group of IBM patients.

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CONFLICT OF INTEREST

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DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

ETHICS STATEMENT

We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

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